Technical Abstract
Simon J. Hall, PI
Phase I Trial of Adenovirus-Mediated IL-12 Gene Transduction in Patients with Radiorecurent Prostate Cancer

Background: Patients with radiorecurrent prostate cancer have few options. Success of salvage therapies is limited due to the presence of locally extensive disease and/or the presence of undetected metastatic disease. Gene therapy may define a treatment option of both local and systemic value. Pre-clinical studies using adenovirus-mediated (Ad.) transduction of IL-12 (Ad.mIL-12) in an aggressive metastatic model of prostate cancer illustrated the potential benefit of this therapy in this patient population. Injection of an established primary tumor resulted in local growth suppression, survival enhancement and inhibition of pre-established metastases. The basis for these activities include the induction of both innate (neutrophils & NKs) and acquired immunity (T cells) and the upregulation of tumor cell expression of Fas to increase killing through the Fas/FasL pathway.

Objectives/Hypohesis: On the basis of these results, we propose to explore the use of Ad.hIL-12 in patients with clinically localized radiorecurrent prostate cancer in a Phase I trial to explore the safety, induction of immune responses and efficacy following therapy.

Specific Aims/Study Design:

In **Aim I** patients will be placed in escalating dose cohorts with the primary endpoint of the maximum tolerated dose as determined by physical examination, laboratory values of bodily functions and evidence of IL-12 gene transduction by measurement of serum by ELISA.

In **Aim 2** additional safety data will be recorded through measurement of serum levels of the pro-inflammatory cytokines, TNF-α, IFN-γ and IL-16 by ELISA.

In **Aim 3** peripheral blood mononuclear cells (PBMCs) will be screened for the induction of NK cells and T cells, which target the prostate antigens, PSA and PAP via an ELISPOT assay.

In **Aim 4** evidence of efficacy will be suggested from monitoring of serum PSA.

Relevance:
In summary this trial is designed thoroughly test the safety of Ad.hIL-12 gene therapy in patients with few viable options. In addition studies will correlate immune end points noted to mediate anti-tumor activity in animal models and infer efficacy through monitoring of PSA. The results of this trial in terms of safety, efficacy and induction of immune responses will dictate future pre-clinical work and future combination gene therapy clinical trials.